1.3.1.1.3 Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ZEPTRALI CR 200

ZEPTRALI CR 400

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZEPTRALI CR 200

Each controlled-release tablet contains 200 mg Carbamazepine

Sugar free

ZEPTRALI CR 400

Each controlled-release tablet contains 400 mg Carbamazepine

Sugar free

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Controlled- release tablet

ZEPTRALI CR 200

Yellowish orange, oval shaped, slightly biconvex, coated tablets with a score line on each side.

ZEPTRALI CR 400

Brownish orange, oval shaped, slightly biconvex, coated tablets with a score line on each side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Epilepsy with motor and psychic manifestations:
  - psychomotor or temporal-lobe epilepsy
  - generalized tonic-clonic seizure
  - mixed forms of seizures
  - complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalisation.
- Acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.
- Idiopathic trigeminal neuralgia.
- Idiopathic glossopharyngeal neuralgia.

ZEPTRALI CR is suitable for both monotherapy and combination therapy.

ZEPTRALI CR is usually not effective in absences (petit mal) and myoclonic seizures. (See section **4.4**).

4.2 Posology and method of administration

Posology

As a result of slow, controlled release of the active substance from the CR tablets, these are designed to be taken in a twice daily dosage regimen.

Dosage should be as low as is consistent with a satisfactory effect. Blood plasma levels can be used to help establish the optimum dose. In the treatment of epilepsy, the dose of **ZEPTRALI CR** usually requires total plasma-carbamazepine concentrations of about 4 to 12 µg/ml (17 to 50 µmol/liter).

When the patient is transferred from another anticonvulsant medicine to **carbamazepine**, the dosage of the first should be reduced gradually.

Switching patients from conventional tablets to controlled release (CR) tablets: reported clinical experience shows that in some patients the dosage in the form of CR tablets may need to be increased.

Due to interactions and different anti-epileptic medicine pharmacokinetics, the dosage of **carbamazepine** as in **ZEPTRALI CR** should be selected with caution in elderly patients.

Epilepsy

When possible, **ZEPTRALI CR** should be prescribed as monotherapy.

Treatment should be initiated with a low daily dosage, to be slowly increased until an optimal effect is obtained.

Determination of plasma levels may help in establishing the optimum dosage.

When **ZEPTRALI CR** is added to existing anti-epileptic therapy, this should be done gradually while maintaining, or if necessary adapting, the dosage of the other anti-epileptic(s). (See section **4.5**).

Usual dosage for adults

Initially, 100 mg to 200 mg once or twice a day, followed by a slow increase until usually at a level of 400 mg twice or three times a day, the best response is obtained. In some instances 1600 mg in 3 to 4 divided doses may be necessary.

Trigeminal Neuralgia and glossopharyngeal neuralgia

The initial dosage of 200 - 400 mg should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 - 4 times daily, in some instances it may necessitate 1600 mg daily). The dosage should then be gradually reduced to the lowest possible maintenance level. In elderly and

particularly sensitive patients (see section **4.4**) an initial dosage of 100 mg twice a day is recommended.

Acute mania and maintenance treatment of(bipolar) affective disorders

Dosage range:

Approximately 400 - 1600 mg daily, the usual dosage being 400 –

600 mg daily given in 2 -3 divided doses. In acute mania, the dosage should be increased rather quickly, whereas small dosage increments are recommended for maintenance therapy of bipolar disorders in order to ensure optimal tolerability.

Method of administration

For oral use.

The **ZEPTRALI CR** tablets may be taken during, after, or between meals.

The **ZEPTRALI CR tablets** should be swallowed whole with adequate amount of fluid.

4.3 Contraindications

- Known hypersensitivity to carbamazepine, or structurally related medicines e.g. tricyclic antidepressants, or any other component of the formulation (See section 6.1)
- Patients with atrioventricular block
- Patients with a history of bone marrow depression
- Patients with a history of porphyria (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda)

- The use of **ZEPTRALI CR** is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs) or within 2 weeks of discontinuation of MAOIs (see section **4.5**).

- The active substance of **ZEPTRALI CR** passes into the breast milk (about 25 - 60 % of plasma concentration). Mothers taking **ZEPTRALI CR** should not breastfeed their infants.

  Previous Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

4.4. Special warnings and precautions for use

Patients should be made aware of early toxic signs and symptoms of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult the medical practitioner immediately.

Medical supervision during treatment is essential.

Haematological effects

Aplastic anaemia and agranulocytosis have been reported; however, due to the very low incidence of these conditions, meaningful risk estimates for carbamazepine are difficult to obtain.

Transient or persistent decreased platelet or white blood cell counts may occur; in the majority of cases these effects prove transient. Complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline and periodically thereafter.

Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult the medical practitioner immediately.

If the white blood cell or platelet count is definitely low or decreased during the treatment, the patient and the complete blood count should be closely monitored (see **section 4.8**). However, treatment

with **ZEPTRALI CR**–should be discontinued if the patient develops leucopenia which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. **ZEPTRALI CR** should be discontinued if any evidence of significant bone-marrow depression appears.

Serious dermatological reactions

Serious dermatologic reactions, including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome) and Stevens-Johnson syndrome (SJS), have been reported with carbamazepine. Patients with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with carbamazepine. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, TEN) appear, carbamazepine should be withdrawn at once and alternative therapy should be considered. (See section **4.3**).

Immune-mediated ADR's

There is growing reported evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions.

Association with HLA-A*3101 allele

Human Leukocyte Antigen (HLA)-A*3101 may be a risk factor for the development of cutaneous adverse drug reactions such as SJS, TEN, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and maculopapular rash.

Retrospective genome-wide studies in Japanese and Northern European populations reported association between severe skin reactions (SJS, TEN, DRESS, AGEP and maculopapular rash) associated with carbamazepine use and the presence of the HLA-A*3101 allele in these patients.

The frequency of the HLA-A*3101 allele varies widely between ethnic populations, with a frequency between 5 - 15 %. A prevalence of
10 -15 % has been reportedly estimated in some ethnic groups.

Testing for the presence of HLA-A*3101 allele should be considered in patients with ancestry in genetically at-risk populations (for example, patients of the Japanese and Caucasian populations, patients who belong to the indigenous populations of the Americas, Hispanic populations, people of southern India, and people of Arabic descent), prior to initiating treatment with **ZEPTRALI CR**.

The use of **ZEPTRALI CR** should be avoided in patients who are found to be positive for HLA-A*3101.

Screening is generally not recommended for any current carbamazepine users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status.

HLA-B*1502 allele

Retrospective studies in patients of Han Chinese ancestry found a strong correlation between SJS/TEN skin reactions associated with **ZEPTRALI CR** and the presence in these patients of the Human Leukocyte Antigen HLA-B*1502 allele. The frequency of HLA-B*1502 allele ranges from 2 to 12 % in Han Chinese populations and is about 8 % in Thai populations. Higher reporting rates of SJS (rare rather than very rare) are reported in some countries in Asia (e.g. Taiwan, Malaysia and the Philippines) in which there is a higher frequency of the HLA-B*1502 allele in the population (e.g. above 15 % in the Philippines and some Malaysian populations).

Allele frequencies up to about 2 % and 6 % have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in persons of European descent, several

African populations, indigenous people of the Americas, Hispanic populations sampled and in Japanese (< 1 %).

The allele frequencies listed here, represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e. the “carrier frequency”) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

Testing for the presence of HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with ZEPTRALI CR.

The use of **ZEPTRALI CR** should be avoided in tested patients who are found to be positive for HLA-B*l502. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic medicines associated with SJS/TEN. Consideration should therefore be given to avoiding use of other medicines associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low. Screening is generally not recommended for any current carbamazepine users, as the risk of SJS1/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.
The identification of subjects carrying the HLA-B*1502 allele and the avoidance of **ZEPTRALI CR** therapy in these subjects has been reported to decrease the incidence of **ZEPTRALI CR** carbamazepine-induced SJS/TEN.

Genetic screening results must never substitute for appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B* 1502 and treated with **ZEPTRALI CR** will not develop SJS/TEN and patients negative for HLA-B*1502 of any ethnicity can still develop SJS/TEN. Similarly many patients positive for HLA-A*3101 and treated with **ZEPTRALI CR** may not develop severe cutaneous side-effects and patients negative for this allele can still develop them.
The role of other possible factors in the development of, and morbidity from, these severe cutaneous side-effects, such as other anti-epileptic medicines dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for the Healthcare professionals

When testing for the presence of the HLA-B*1502 allele, high resolution "HLA-B*l502 genotyping" is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

Similarly, if testing for presence of the HLA-A*3101 allele should be performed, high-resolution "HLA-A*3101 genotyping" respectively is recommended. The test is positive if either one or two HLA-A*3101 alleles are detected and negative if no HLA-A*3101alleles are detected.

Other dermatologic reactions

Skin reactions, e.g. macular or maculopapular exanthema, can also occur.
However, since it may be difficult to differentiate the early signs of more serious skin reactions from less severe skin reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing **ZEPTRALI CR**.
The HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from **ZEPTRALI CR**, such as anticonvulsant hypersensitivity syndrome or non-serious

rash (maculopapular eruption). However the HLA-B*1502 allele has not been found to predict the risk of these aforementioned skin reactions.

Hypersensitivity

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been reported with **ZEPTRALI CR**. If a patient develops these reactions after treatment with **ZEPTRALI CR**, the medicine must be discontinued, and an alternative treatment started.

ZEPTRALI CR may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon) (see **section 4.8).**

The HLA-A*3101 allele has been found to be associated with the occurrence of hypersensitivity syndrome, including maculopaoular rash.

Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone and phenobarbital).

If signs and symptoms of hypersensitivity reactions occur, **ZEPTRALI CR** should be withdrawn immediately.

Seizures

ZEPTRALI CR should be used with caution in patients with mixed seizures, which includes absences, either typical or atypical. In all these conditions, **ZEPTRALI CR** may exacerbate seizures. In the event of exacerbation of seizures, **ZEPTRALI CR** should be discontinued.

Hepatic function

Liver function tests should also be undertaken periodically. If allergic skin reactions occur, if the platelet count diminishes, if tests reveal deterioration in liver function, or if any serious adverse symptoms develop, **ZEPTRALI CR** should be withdrawn.

Renal function

Baseline and periodic complete urinanalysis and blood urea determinations are recommended.

ZEPTRALI CR should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic, or renal damage, adverse haematological reactions to other medicines, or interrupted courses of therapy with **ZEPTRALI CR**.

Hyponatraemia

Hyponatraemia is reported to occur with **ZEPTRALI CR**. In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating **ZEPTRALI CR** therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors

may apply especially to elderly patients. If hyponatraemia is observed, water restriction is an important counter-measurement if clinically indicated.

Hypothyroidism

ZEPTRALI CR may reduce serum concentrations of thyroid hormones through enzyme induction requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism. Hence, thyroid function monitoring is suggested to adjust the dosage of thyroid replacement therapy.

Anticholinergic effects

ZEPTRALI CR has been reported to show mild anticholinergic activity. Patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy (see section **4.8**).

Other

Medical supervision during treatment is essential.

Abnormalities of liver function and jaundice have been reportedly associated with long-term treatment.

Liver function tests should also be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease.

Some liver function tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyltransferase. This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication for the withdrawal of carbamazepine.

Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment with **ZEPTRALI CR** suspended pending the outcome of the evaluation.

Carbamazepine should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with carbamazepine.

Baseline and periodic complete urinalysis and BUN determinations are recommended.

Psychiatric effects

The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicines such as **ZEPTRALI CR** in several indications. A reported meta-analysis of randomized placebo-controlled trials of antiepileptic medicines has shown an increased risk of suicidal ideation and behaviour. The mechanism of this risk is not reported. Therefore patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Pregnancy and females of reproductive potential

ZEPTRALI CR may be associated with foetal harm when administered to a pregnant woman (see **section 4.6**).

Adequate counselling should be made available to all pregnant women and women of childbearing potential, regarding the risks associated with pregnancy due to potential teratogenic risk to the foetus (see section **4.6**).

Women of childbearing potential should use effective contraception unaffected by enzyme inducing medicines, during treatment with **ZEPTRALI CR** and for a period of 28 days after discontinuation of treatment (see section 4.6).

Prenatal exposure to **ZEPTRALI CR** may increase the risks for major congenital malformations and other adverse development outcomes (see **section 4.6**). **ZEPTRALI CR** should be used during pregnancy only if the potential benefit justifies the potential risks.

Women of childbearing potential should be fully informed of the potential risk to the foetus if they take carbamazepine during pregnancy. Women of childbearing potential should be counselled to contact the doctor immediately if they become pregnant or think they might be pregnant and are taking carbamazepine.

Before the initiation of treatment with carbamazepine in a woman of childbearing potential, pregnancy testing should be considered.

Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should use effective contraception unaffected by enzyme inducing drugs, during treatment with carbamazepine and for a period of 28 days after discontinuation of treatment (see section **4.6**).

Endocrinological effects

Breakthrough bleeding has been reported in women taking hormonal contraceptives; the reliability of hormonal contraceptives may be adversely affected by **ZEPTRALI CR**, and women of

childbearing age should be advised to consider using alternative forms of birth control while taking **ZEPTRALI CR**.

Patients taking carbamazepine and requiring hormonal contraception should receive a preparation containing not less than 50µg oestrogen or use of some alternative non-hormonal method of contraception should be considered.

Dose reduction and withdrawal effects

Tolerance may develop to some of the untoward effects of **ZEPTRALI CR**. These effects can be minimised by gradual increase in dosage and adjustment to the lowest effective maintenance dosage.

Abrupt withdrawal of **ZEPTRALI CR** may precipitate seizures, therefore carbamazepine should be withdrawn gradually over a 6-month period. If treatment with **ZEPTRALI CR** has to be withdrawn abruptly in a patient with epilepsy, the change-over to the new anti-epileptic medicine should be made under cover of a suitable medicine (e.g. diazepam or phenytoin).

Falls

ZEPTRALI CR treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedation (see **section 4.8**) which may lead to falls and, consequently fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete risk assessment of fall should be considered recurrently for patients on long-term **ZEPTRALI CR** carbamazepine treatment.

Monitoring of plasma levels

Although correlations between dosages and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous**,** monitoring of the plasma levels may be useful in the following conditions: dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used (see section **4.5**)

Interactions

Co-administration of inhibitors of CYP3A4 or inhibitors of epoxide hydrolase with carbamazepine can induce adverse reactions (increase of carbamazepine or carbamazepine-10,11 epoxide plasma concentrations, respectively). The dosage of **ZEPTRALI CR** should be adjusted accordingly and/or the plasma levels monitored.

Co-administration of CYP3A4 inducers with carbamazepine may decrease carbamazepine plasma concentrations and its therapeutic effect, while discontinuation of a CYP3A4 inducer may increase carbamazepine plasma concentrations. The dosage of **ZEPTRALI CR** may have to be adjusted.

ZEPTRALI CR is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism. (See section **4.5**).

Female patients of child-bearing potential should be warned that the concurrent use of **ZEPTRALI CR** with hormonal contraceptives may render this type of contraceptive ineffective (see sections **4.5** and **4.6**). Alternative non-hormonal forms of contraception are recommended when using carbamazepine.

ZEPTRALI CR contain sodium

This medicine contains less than 1mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P4503A (CYP3A4) is the main enzyme catalyzing formation of the active metabolite carbamazepine-10,11-epoxide. Co-administration of inhibitors of CYP3A4 may result in increased plasma concentrations, which could induce adverse reactions. Co-administration of CYP3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to a potential decrease in carbamazepine serum level and potential decrease in the therapeutic effect.

Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels.

Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolised by CYP3A4 by induction of their metabolism.
Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11-epoxide. Coadministration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11-epoxide plasma concentrations. Such inhibitors are valproic acid, valpromide, valnoctamide and progabide.

Interactions resulting in a contraindication

The use of carbamazepine is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering carbamazepine MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits.

Medicines that may raise carbamazepine plasma levels

Since raised plasma carbamazepine levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below.

Analgesics, anti-inflammatory medicines: ibuprofen, dextropropoxyphene

Androgens: danazol

Antibiotics: macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin) and ciprofloxacin

Antidepressants: desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine, trazodone, viloxazine

Antiepileptics: stiripentol, vigabatrin

Antifungals: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole). Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole.

Antihistamines: terfenadine

Antipsychotics: olanzapine

Antituberculosis: isoniazid

Antivirals: protease inhibitors for HIV treatment (e.g. ritonavir)

Carbonic anhydrase inhibitors: acetazolamide

Cardiovascular medicines: diltiazem, verapamil

Gastrointestinal medicines: cimetidine, omeprazole

Muscle relaxants: oxybutynin, dantrolene

Platelet aggregation inhibitors: ticlopidine

Other interactions: grapefruit juice, nicotinamide (only in high dosage)

Medicines that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels.

Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of **ZEPTRALI CR** should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide, brivaracetam and valpromide.

Medicines that may decrease carbamazepine and/or carbamazepine-10,11-epoxide plasma levels

The dose of carbamazepine may have to be adjusted when used concomitantly with the substances described below:

Antiepileptics: felbamate, methsuximide, oxcarbazepine, phenobarbitone, phensuximide, phenytoin (to avoid phenytoin intoxication and sub therapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 µg/ml before adding carbamazepine to the treatment) and primidone and, although the reported data are partly contradictory, possibly also clonazepam

Antineoplastics: cisplatin or doxorubicin

Antituberculosis: rifampicin

*Bronchodilators o*r anti-asthma medicines: theophylline, aminophylline

Dermatological medicines: isotretinoin

Other interactions: herbal preparations containing St John's wort (*Hypericum perforatum*)

Effect of carbamazepine on plasma levels of concomitant medicines

ZEPTRALI CR may lower the plasma level, or diminish - or even abolish - the activity of certain medicines. The dosage of the following medicines may have to be adjusted to clinical requirements:

Analgesics, anti-inflammatory agents: buprenorphine, methadone, paracetamol (long term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity), tramadol

Antibiotics: doxycycline, rifabutin

Anticoagulants: oral anticoagulants (e.g. warfarin, acenocoumarol, rivaroxaban, apixaban and edoxaban and others e.g. dabigatran)

Antidepressants: bupropion, citalopram, mianserin, sertraline, nefazodone, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine). The use of **ZEPTRALI CR** is contra-indicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering **ZEPTRALI CR**, MAOIs should be discontinued for a minimum of 2 weeks or longer, if the clinical situation permits. (See section **4.3**).

Antiemetics: aprepitant

Antiepileptics: clobazam, clonazepam, ethosuximide, eslicarbazepine, oxcarbazepine, felbamate, lamotrigine, primidone, tiagabine, topiramate, valproic acid, zonisarnide. There have been reports of an increase in plasma mephenytoin levels. To avoid phenytoin intoxication and and subtherapeutic concentrations of carbamazepine, it is recommended to adjust the plasma concentration of phenytoin to 13 µg/ml before adding **ZEPTRALI CR** to the treatment.

Antifungals: itraconazole, voriconazole. Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole.

Antihelmintics: praziquantel, albendazole

Antineoplastics: imatinib; cyclophosphamide, lapatinib, temsirolimus

Antipsychotics: clozapine, haloperidol and bromperidol, quetiapine, risperidone, ziprasidone, olanzapine, aripiprazole, paliperidone

*Antivirals:*protease inhibitors for HIV treatment (e.g. indinavir, ritonavir, saquinavir).

Anxiolytics: alprazolam, midazolam

Bronchodilators or anti-asthma medicines: theophylline

Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered)

Cardiovascular medicines: calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine

Corticosteroids: corticosteroids (e.g. prednisolone, dexamethasone)

Medicines used in erectile dysfunction: tadalafil

Immunosuppressants: ciclosporin, everolimus, tacrolimus, sirolimus

Thyroid agents: levothyroxine.

Other drug interactions: products containing oestrogens and/or progesterones.

The level of serum folic acid should be observed during anticonvulsant therapy since **ZEPTRALI CR** may enhance the metabolism of folic acid.

Combinations that require specific consideration

Concomitant use of **ZEPTRALI CR** and levetiracetam has been reported to increase carbamazepine-induced toxicity.

Concomitant use of **ZEPTRALI CR** and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

Combined use of **ZEPTRALI CR** and lithium, or metoclopramide on the one hand, and carbamazepine and neuroleptics (haloperidol, thioridazine) on the other, may lead to increased neurological adverse reactions (with the latter combination even in the presence of 'therapeutic plasma levels').

Concomitant medication with **ZEPTRALI CR** and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.

ZEPTRALI CR may antagonise the effects of non-depolarising muscle relaxants (e.g. pancuronium); their dosage may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.

ZEPTRALI CR may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol during treatment.

Concomitant use of **ZEPTRALI CR** with direct acting oral anti-coagulants (rivaroxaban, dabigatran, apixaban and edoxaban) may lead to reduced plasma concentrations of direct acting oral anti-coagulants, which carries the risk of thrombosis. Therefore, if a concomitant use is necessary, closer monitoring of signs and symptoms of thrombosis is recommended.

Interference with serological testing

ZEPTRALI CR may result in false positive perphenazine concentrations in HPLC analysis due to interference.

ZEPTRALI CR and the 10,11-epoxide metabolite may result in false positive tricyclic antidepressant concentration in fluorescence polarized immunoassay method.

4.6. Fertility, pregnancy and lactation

Pregnancy:

Safety of **ZEPTRALI CR** in pregnancy has not been demonstrated.

Patients should consult their medical practitioner for guidance on the use of **ZEPTRALI CR** during pregnancy.

Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. There are reports of developmental disorders and malformations, including spina bifida and hypospadias in association with **ZEPTRALI CR**.

Neurodevelopmental disorders have been reported among children born to women with epilepsy treated with carbamazepine alone or in combination with other antiepileptic medicines during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to carbamazepine during pregnancy are contradictory and a risk cannot be excluded.

- If women receiving **ZEPTRALI CR** become pregnant or plan to become pregnant, or if the need of initiating treatment with **ZEPTRALI CR** arises during pregnancy, the medicine's expected benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy.
- In women of childbearing potential **ZEPTRALI CR** should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women

treated with a combination of antiepileptic medicines is greater than in those of mothers receiving the individual medicines as monotherapy. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific medicines used and may be higher in polytherapy combinations that include valproate.

- Minimum effective doses should be given and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range (4 to 12 µg/ml) provided seizure control is maintained. There is evidence to suggest that the risk of malformation with **ZEPTRALI CR** may be dose-dependent, i.e. at a dose < 400 mg per day, the rates of malformation were lower than with higher doses of carbamazepine.

- Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

- During pregnancy, an effective antiepileptic treatment should not be interrupted, since aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention

Folic acid deficiency is known to occur in pregnancy. Anti-epileptic medicines have been reported to aggravate folic acid deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy.

In the neonate

In order to prevent bleeding disorders in the offspring, it is also recommended that vitamin K_1 be given to the mother during the last weeks of pregnancy as well as to the neonate.

Cases of neonatal seizures and/or respiratory depression associated with maternal **ZEPTRALI CR** and other concomitant anticonvulsant medicine use have been reported. Cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal **ZEPTRALI CR** use. These reactions may represent a neonatal withdrawal syndrome.

Women with manic depressive (bipolar) disorders have an increased risk to relapse during pregnancy and/or the post partum period.

Lactation:

Carbamazepine passes into breast milk (about 25 to 60 % of plasma concentrations). Mothers on **ZEPTRALI CR** should not breastfeed their infants.

Fertility:

There have been reports of impaired male fertility and/or abnormal spermatogenesis.

Contraception

Women of childbearing potential should use effective contraception during treatment with **ZEPTRALI CR** and for 2 weeks after the last dose. Due to enzyme induction, **ZEPTRALI CR** may result in a failure of the therapeutic effect of oral contraceptive medicines containing oestrogen and/or progesterone. Therefore, women of child-bearing potential should be advised to use alternative contraceptive methods while on treatment with **ZEPTRALI CR**.

4.7 Effects on ability to drive and use machines

Reaction time may be decreased by carbamazepine resulting in seizures and adverse reactions including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision have been reported with carbamazepine, especially at the start of treatment or in connection with dose adjustments.

Patient should therefore exercise due caution when driving a vehicle or operating machinery.

4.8. Undesirable effects

a) Summary of the safety profile

Particularly at the start of treatment with carbamazepine, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reactions occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia); gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions. Dose-related adverse reactions may abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels.

b) Tabulated summary of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Blood and lymphatic system disorders	Leukopaenia, thrombocytopaenia, eosinophilia	anaphylactic reaction, oedema angioedema, hypogammaglobulin-aemia. leukocytosis,	bone marrow depression

		lymphadenopathy, agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, reticulocytosis, haemolytic anaemia	
Immune system disorders		a delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo-lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests and vanishing bile duct syndrome (destruction of disappearance of the intrahepatic bile ducts), occurring in various combinations. Other organs may also be	anaphylactic reaction, angioedema, hypogammaglo-bulinaemia **drug rash with eosinophilia and systemic symptoms (DRESS)

		affected (e.g. lungs, kidneys, pancreas, myocardium, colon)	
Infections and infestations			**reactivation of Human herpes virus 6 infection.
Endocrine disorders	oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusion, neurological disorders	galactorrhoea, gynaecomastia	
Metabolism and nutrition disorders		Folate deficiency, decreased appetite, porphyria acute (acute intermittent porphyria and	Hyperammonaemia

		variegate porphyria), porphyria non-acute (porphyria cutanea tarda).	
Psychiatric disorders		hallucinations (visual or auditory), depression, aggression, agitation, restlessness confusional state activation of psychosis	
Nervous system disorders	dizziness, ataxia, somnolence, headache, diplopia,	abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics); nystagmus, dyskinesia, eye movement disorders, speech disorders (e.g. dysarthria, slurred speech), choreoathetosis, peripheral neuropathy, paraesthesia, paresis neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia	**sedation, memory impairment

Eye disorders	accommodation disorders (e.g. blurred vision	lenticular opacities, conjunctivitis,	
Ear and labyrinth disorders		hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception	
Cardiac disorders		cardiac conduction disorders, dysrhythmia, atrioventricular block with syncope, bradycardia, congestive cardiac failure, aggravation of coronary artery disease	
Vascular disorders		Hypertension or hypotension, circulatory collapse, embolism (e.g. pulmonary embolism), Thrombophlebitis	
Respiratory, thoracic and mediastinal disorders		pulmonary hypersensitivity characterized e.g. by fever, dyspnoea, pneumonitis or pneumonia	

Gastrointestinal disorders	nausea, vomiting dry mouth, with suppositories rectal irritation may occur	diarrhoea, constipation, abdominal pain, glossitis, stomatitis, pancreatitis	colitis
Hepatobiliary disorders		Hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice, hepatic failure, granulomatous liver disease	
Skin and subcutaneous tissue disorders	allergic dermatitis, urticaria which may be severe	exfoliative dermatitis, systemic lupus erythematosus, pruritus Stevens-Johnson syndrome*, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme and erythema nodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism	Acute Generalized Exanthematous Pustulosis (AGEP)**, lichenoid keratosis, onychomadesis.

Musculoskeletal and connective tissue disorders		muscular weakness, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/ osteoporosis, arthralgia, myalgia, muscle spasms	fracture
Renal and urinary disorders		tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria, and increased blood urea /azotemia), urinary frequency, urinary retention	
Reproductive system		Sexual dysfunction/erectile dysfunction, abnormal spermatogenesis (with decreased sperm count and/or motility	
General disorders and administration site conditions	fatigue		

Investigations	gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant, blood alkaline phosphatase increased	transaminases increased, intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased	bone density decreased
Injury, poisoning and procedural complications			Fall (associated with carbamazepine treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation)

			(see section 4.4 warning and precautions).

* In some Asian countries also reported as rare. See **section 4.4.** Special warnings and precautions for use.

**Additional adverse drug reactions from spontaneous reports (frequency not known).

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with carbamazepine. The mechanism by which carbamazepine affects bone metabolism has not been identified.

There is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous ADRs such as SJS, TEN, DRESS, AGEP and maculopapular rash. In Japanese and European patients, these reactions have been reported to be associated with the use of carbamazepine and the presence of the HLA-A*3101 allele. Another marker, HLAB* 1502 has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry (see sections 4.2 and 4.4 for further information).

c) Description of selected adverse reactions

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with carbamazepine. The mechanism by which carbamazepine affects bone metabolism has not been identified.

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use of carbamazepine and the presence of the HLA-A*3101 allele. Another marker, HLA-B*1502 has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry (see sections **4.2 and 4.4** for further information).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Suspected adverse reactions can also be reported directly to the HCR via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000.

4.9. Overdose

The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular, and respiratory systems.

Central nervous system

CNS depression, disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma, blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyper-reflexia, later hyporeflexia, convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis

Respiratory system

Respiratory depression, pulmonary oedema

Cardiovascular system

Tachycardia, hypotension, at times hypertension, conduction disturbance with widening of ORS complex; syncope in association with cardiac arrest

Gastrointestinal system

Vomiting, delayed gastric emptying, reduced bowel motility

Musculoskeletal system

Cases of rhabdomyolysis has been reported in association with carbamazepine toxicity

Renal function

Retention of urine, oliguria or anuria, fluid retention, water intoxication due to an ADH-like effect of carbamazepine.

Laboratory findings

Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatine phosphokinase.

Treatment

No specific antidote. Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm carbamazepine poisoning and to ascertain the size of the overdose. Administration of activated charcoal. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations

Charcoal haemoperfusion has been recommended. Haemodialysis is the effective treatment modality in the management of carbamazepine overdose.

Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.5 Anticonvulsants, including anti-epileptics.

Therapeutic class: antiepileptic, neurotropic, and psychotropic agent; (ATC Code: N03 AF01).

Mechanism of action

Carbamazepine possesses both anticonvulsant and psychotropic properties.

5.2. Pharmacokinetic properties

Absorption

Carbamazepine is absorbed relatively slowly from the tablet. Peak plasma concentrations are attained 4 to 24 hours after a single oral dose. The CR 200 tablets yield a mean peak plasma

concentration of the carbamazepine within 24 hours, while for the suspension, mean peak plasma concentrations are attained within 2 hours.

There is no clinically relevant difference between the quantity of carbamazepine absorbed from the various dosage forms.

The carbamazepine CR tablets provide more stable plasma concentrations throughout the day, thereby allowing twice daily dosage.

Distribution

Carbamazepine is 70 – 80 % bound to plasma proteins. The concentration of carbamazepine in the saliva reflects the unbound fraction in the plasma (20 to 30 %).

Elimination

The elimination half-life of carbamazepine is approximately 36 hours after a single oral dose, whereas after repeated administration, which leads to auto induction of hepatic enzymes, it averages only 16 to 24 hours, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme inducing anti-epileptic medicines, half-life values averaging 9 to 10 hours have been found.

Only 2 to 3 % of the dose is excreted in the urine in unchanged form. The primary metabolite is the pharmacologically active carbamazepine-10,11-epoxide.

Biotransformation

Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the carbamazepine-10,11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 is responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine, while the microsomal epoxide hydrolase enzyme is responsible for the formation of the carbamazepine-10,11-transdiol derivative from carbamazepine-10,11-epoxide.

The steady-state plasma concentrations of carbamazepine considered as in the 'therapeutic range', vary considerably interindividually: for the majority of patients a range between 4 - 12 µg/ml corresponding to 17 - 50 µmol/l has been reported.

Special populations

Paediatric patients

Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults.

Geriatric patients (65 years or above)

There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.

Patients with hepatic or renal impairment

No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbamazepine granules

Isopropyl alcohol, povidone (K-30), purified water.

Intragranular materials

Colloidal anhydrous silica, eudragit NE 30D, ethylcellulose aqueous dispersion (aquacoat ECD 30), purified water.

Pre Lubrication

Microcrystalline cellulose pH102, croscarmellose sodium, talc, povidone (K-30), colloidal anhydrous silica, magnesium stearate.

Film-Coating

Hypromellose (HPMC E-5), macrogolglycerol hydroxystearate 40, titanium dioxide [E171], talc, iron oxide red [E172], iron oxide yellow [E172], purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from moisture.

Return all unused or expired medicines to your pharmacist for safe disposal.

Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

6.5 Nature and contents of container

12 Tablets are packed in one Alu/PVC/PVDC Blister. One such blister (1 x 12's) packed in a carton.

10 Tablets are packed in one Alu/PVC/PVDC Blister. Three such blisters (3 x 10's) packed in a carton.

500 Tablets are packed in a white HDPE bottle.

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

Zeptrali CR 200: 59/2.5/0811

Zeptrali CR 400: 59/2.5/0812

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 July 2026

10 DATE OF REVISON OF THE TEXT

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